Kaleidoscope

Volume 10 Article 4

June 2012

The Role of D1 Dopamine Receptors on Incentive Salience Attribution

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Introduction

When a neutral stimulus cue is followed by a reward, an association develops between the cue and reward. The cue, a conditioned stimulus (CS), becomes a predictor of the reward, an unconditioned stimulus (US). Repeated pairing of the CS-US elicits a conditioned response (CR). This associative learning is called Pavlovian conditioning. Through Pavlovian learning, an individual can come to attribute incentive motivational properties towards the reward-associated stimulus. This is called "incentive salience" where the stimulus becomes attractive and wanted, in a sense, becoming a motivational magnet (Robinson and Berridge, 2001).

Research has shown that individual differences in incentive salience attribution have been linked with drug abuse-like behavior (Flagel et al., 2008). Pavlovian conditioned approach (PCA) has been used as a primary measure of incentive salience. Within a PCA task, a CS is presented for a few seconds and then removed; the US is then delivered immediately, regardless of the behavior. Incentive salience is measured within the PCA task by measuring the differential responses that are displayed towards the CS. Rats that attribute incentive value to the CS will approach and make contact with it; these animals are called "sign-trackers". On the contrary, rats that treat the CS as a simple signal of a forthcoming reward will approach the location of reward delivery; these animals are called "goal-trackers".

Studies have shown that sign-tracking and goal-tracking animals also express differences in relation to abuse-like behaviors. Animals that attribute incentive value to reward-related cues and display sign-tracking behavior are higher novelty seekers (Beckmann et al., 2011), more impulsive (Tomie et al., 1998; Flagel et al., 2010), more likely to initiate cocaine self-administration (Beckmann et al., 2011), more willing to work for a cocaine reinforcer (Saunders and Robinson, 2011), and more susceptible to relapse of cocaine-seeking behavior following a period of abstinence (Saunders and Robinson, 2010, 2011). Moreover, in a recent study, it was shown that dopamine, a neurotransmitter associated with learning and reward (Flagel et al., 2011), plays a major role in the attribution of incentive value to reward-related cues exhibited during sign-tracking behavior; however, the specific dopamine receptors involved in this process are unknown. Given the relationship between sign-tracking and subsequent vulnerability to the initiation and relapse of cocaine self-administration, understanding the receptor systems that mediate this behavior may help in the development of new pharmacotherapies to treat substance abuse disorders. Toward this goal, the current study utilized a selective dopamine D1 receptor antagonist to examine the role of the D1 receptor subtype on the expression of sign- and goal-tracking behavior within a PCA task.

Methods

Animals

Twelve male Sprague Dawley rats were individually housed in a temperature and humidity controlled colony with a 14 to 10 hour light/dark cycle (lights on at 6 am). Food and water was available at all times while the rats were in the colony. Upon arrival all rats were acclimated to the colony environment and handled daily for a week prior to experimentation. During the last

few days of acclimation, rats were given a daily subcutaneous saline injection to habituate them to the injection procedure.

It should be noted that the administration of saline injections to habituate animals to the injection procedure was added in order to control for any stress effects that could have developed in an earlier run of this experiment. It was determined that the novel experience of an injection and placement into a new environment caused animals to develop aversive feelings. This was seen in the PCA training data in which there was no discrimination in response behaviors which called for a rerun.

Apparatus

Pavlovian conditioned approach was conducted within operant conditioning chambers that were enclosed within sound-attenuating compartments. Each chamber was connected to a personal computer interface, and all chambers were operated using MED-PC^{TM}. Each chamber contained a food receptacle, two retractable levers on either side of the food receptacle, and a light above each lever. Sucrose pellets were delivered via a pellet hopper.

Pavlovian Conditioned Approach

Prior to Pavlovian conditioned approach training, rats underwent magazine shaping for two days, where they learned to retrieve sugar pellets from a food receptacle. During these two days, the rats were given a pretreatment, where they received a subcutaneous injection of saline before being placed into an operant chamber. Immediately following magazine training, rats were trained under a PCA task. Fifteen minutes before each PCA session, rats were given a subcutaneous pretreatment of either the D1 receptor antagonist SCH-23390 (0.01 mg/kg) or saline. The dosage for SCH-23390 was determined by a pilot experiment which demonstrated nonspecific suppressive effects on animals. During PCA training, a response lever (counterbalanced across and within groups) was inserted into the chamber for 8s, and following lever retraction, a food pellet was non-contingently delivered into the receptacle. Lever-insertion trials were spaced by a 90-s variable time schedule that began immediately after pellet delivery. Each session consisted of 25 lever insertions, and rats were trained for 5 consecutive days. Sign-tracking responses were recorded as lever presses, while goal-tracking responses were recorded as breaks of a photo beam within the food receptacle.

Cocaine self-administration

Three days after Pavlovian training, rats were anesthetized and jugular catheters were implanted. After one-week of post-surgical recovery all rats were trained to acquire cocaine self-administration. This occurred in two separate 1 hour sessions. During the first session, the active lever (opposite to that used in PCA training) was extended and paired with a 0.25 mg/kg infusion of cocaine 10 different times during the first 15 minutes. For the next 45 minutes, an inactive lever was presented. Following a 1 hour break spent in their home cage back in the colony, rats were then returned to the operant chamber for an FR1 schedule of reinforcement, where each response on the lever resulted in an infusion of cocaine. Responses on the active and inactive lever were recorded during both cocaine sessions.

Analysis

One-way ANOVA was used to analyze the effects of treatment (SCH-23390 or saline) on the average rate of sign-tracking, goal-tracking, and goal-tracking during the ITI from the 5 days of PCA training. A 2-way, mixed-factors ANOVA, with treatment (SCH-23390 or saline) as a between-subject factor and session as a within-subject factor, was used to analyze the effects of treatment on the acquisition of sign-tracking, goal tracking, and goal tracking during the ITI over the 5 consecutive days of PCA training. All *post hoc* analyses were done using Bonferroni-corrected pair wise comparisons.

Results

SCH-23390 significantly affected the rate of sign-tracking responses emitted. Fig.1 illustrates that animals treated with SCH-23390 over the 5 days of PCA training emitted fewer sign-tracking responses than the saline control group [$F(1,8) = 5.11$, $p<0.05$]; they also emitted more goal-tracking responses than the saline control group [$F(1,8) = 25.34$, $p<0.05$], while goal tracking during the ITI did not differ between the two groups.

Fig. 2a illustrates that, relative to the saline control group, animals that were given the SCH-23390 did not learn to sign-track over the course of the 5 day PCA training period. A two-way ANOVA revealed a significant main effect of treatment [$F(1,8) = 5.11$, $p<0.05$], a significant effect of time [$F(4,32) = 3.89$, $p<0.05$], and a significant treatment x time interaction [$F(4,32) = 4.65$, $p<0.05$], indicating that sign-tracking responses increased over the 5 PCA training sessions for animals treated with saline but not for animals treated with SCH-23390. *Post hoc* analysis indicated that saline-treated animals emitted more sign-tracking responding on sessions 3-5. Additionally, Fig. 2b illustrates that, relative to the saline control, animals treated with SCH-23990 learned to goal track, over the course of the 5-day training period. A 2-way ANOVA revealed a significant main effect of treatment [$F(1,8) = 9.97$, $p<0.05$] and a significant effect of time [$F(4,32) = 4.57$, $p<0.05$]. However, there was no significant effect for treatment x time interaction [$F(4,32) = 2.37$, $p>0.05$]. Finally, Fig. 2c illustrates the difference in probability of a sign-tracking or goal-tracking response (sign-tracking probability – goal-tracking probability; 1 = exclusive sign tracking; 0 = indifference; -1 = exclusive goal tracking) over the 5-day PCA training period for both saline- and SCH-23390-treated animals. A 2-way ANOVA revealed no significant main effect of time, but a significant main effect of treatment [$F(1,8) = 7.75$, $p<0.05$] and a significant effect treatment x time interaction [$F(4,32) = 4.08$, $p<0.05$], indicating that the saline-treated animals had a greater propensity to sign track and the SCH-2339-treated animals had a greater propensity to goal track over the 5-day PCA training period. *Post hoc* analysis indicated that response probabilities differed between the treatment groups on sessions 2-5.

Discussion

The attribution of motivational value towards a stimulus or incentive salience has been linked to the neurotransmitter dopamine (Flagel et al., 2011); however, the role of specific dopamine receptors is unknown. In this study, the role of the D1 dopamine receptor was examined using the relative expression of sign- and goal-tracking responding during a PCA task. It was found that, relative to saline controls, when the D1 receptor was blocked with SCH-23390 (0.01 mg/kg), the likelihood of obtaining a sign-tracking response was decreased, and the likelihood of

obtaining a goal-tracking response was increased. These results suggest that the D1 receptor plays an important role in the attribution of incentive salience to reward-associated stimuli. Given that both the SCH-23390- and saline- treated animals responded similarly during the inter-trial interval, the drug treatment did not have nonspecific suppressive effects; thus, the decrease in sign-tracking behavior during the conditioning trial cannot be attributed to nonspecific suppressive effects alone.

As the attribution of incentive salience has been linked to enhance acquisition of cocaine self-administration in rats (Beckmann et al., 2011), the present results suggest that animals pretreated with a D1 dopamine antagonist would be less likely to initiate in cocaine self-administration. During cocaine self-administration, due to the delicate nature of the catheters, a few animals were deemed unfit to finish the experiment and had to be euthanized. The resulting effect in the sample size decreasing could not provide any data analysis. In order to obtain data fit for analysis, the experiment had to be redone with a greater sample size. In addition, recent results have indicated that a non-selective dopamine antagonist specifically decreases sign-tracking responding, leaving goal-tracking behavior unaffected (Flagel et al., 2011). In addition to the D1 receptor, dopamine D2 receptors have also been linked to abuse-like behavior (Carati and Schenk, 2011). Thus, future research is necessary to explore the role of D2 receptor signaling in the attribution of incentive salience to reward-associated stimuli and its subsequent effects on the acquisition of abuse-like behavior, like cocaine self-administration.

References

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Figure Captions

Fig 1.Mean (± SEM) response rate (responses/second; r/s) from the 5-day PCA training period as a function of sign-tracking (ST) and goal-tracking (GT) responses during conditioning trials and GT responses during the ITI for saline- and SCH-23390-treated animals. Asterisk (*) = significance at $p < 0.05$. n = 5/group.

Fig 2. (A) Mean (± SEM) sign-tracking response rate during conditioning trials as a function of training session for saline- and SCH-23390-treated animals (B) Mean (± SEM) goal-tracking response rate during conditioning trials as a function of training session for saline- and SCH-23390-treated animals. (C) Mean (± SEM) difference in probability (probability of a sign-tracking response – probability of a goal-tracking response; 1 = exclusive sign tracking; 0 = indifference; -1 = exclusive goal tracking) as a function of training session for saline- and SCH-23390-treated animals. n = 5/group.

Fig 1.

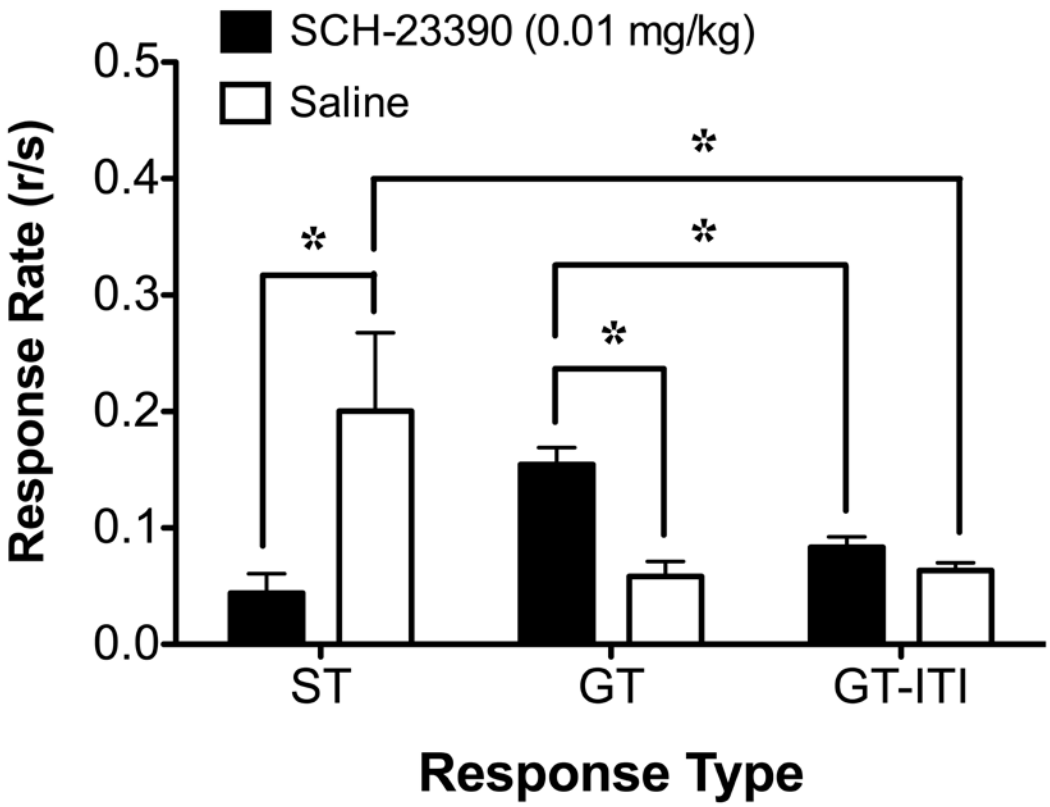
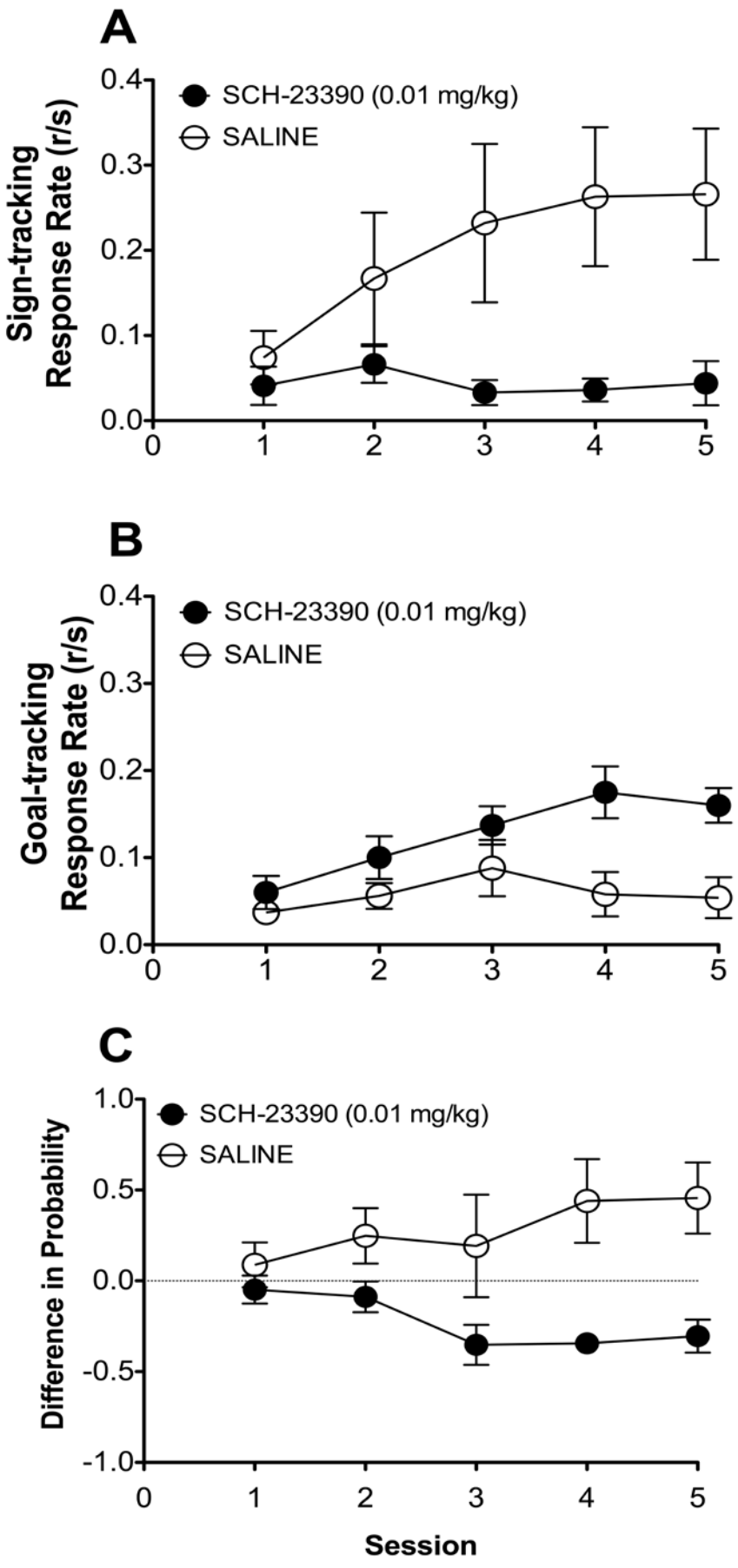

SCH-23390 (0.01 mg/kg)
Saline
Response Rate (r/s)
0.5
0.4
0.3
0.2
0.1
0.0
*
*
*
*
ST
GT
GT-ITI
Response Type

Fig 2.


A
SCH-23390 (0.01 mg/kg)
SALINE
Sign-tracking Response Rate (r/s)
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
B
SCH-23390 (0.01 mg/kg)
SALINE
Goal-tracking Response Rate (r/s)
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
C
SCH-23390 (0.01 mg/kg)
SALINE
Difference in Probability
1.0
0.5
0.0
-0.5
-1.0
0
1
2
3
4
5
Session